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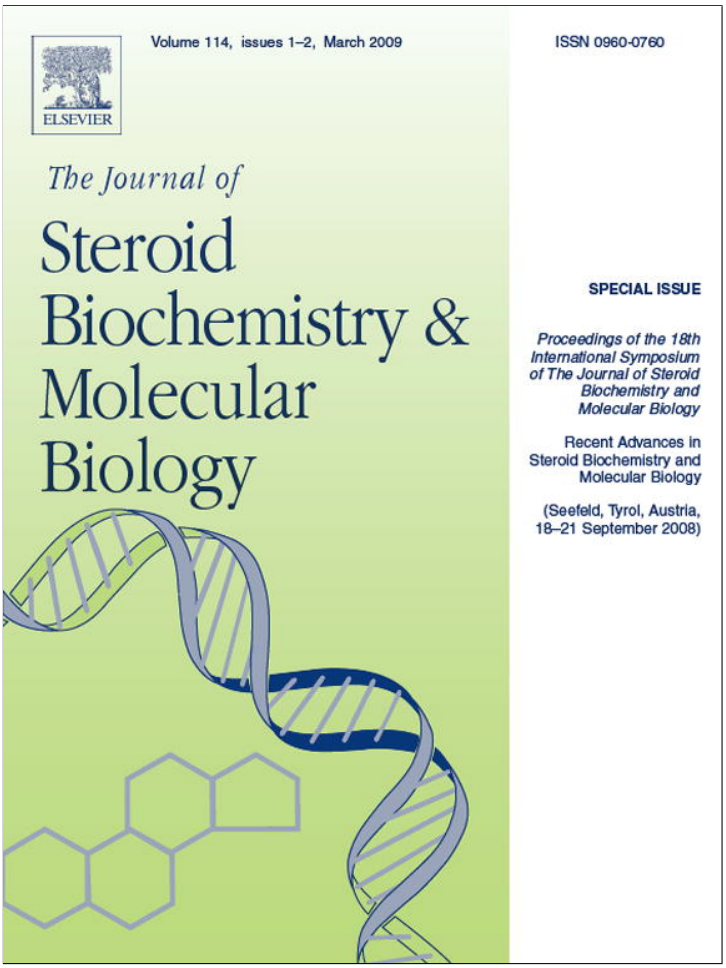

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Vitamin D and aging☆

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ABSTRACT

Recent studies using genetically modified mice, such as FGF23−/− and Klotho−/− mice that exhibit altered mineral homeostasis due to a high vitamin D activity showed features of premature aging that include retarded growth, osteoporosis, atherosclerosis, ectopic calcification, immunological deficiency, skin and general organ atrophy, hypogonadism and short lifespan. The phenotype reversed by normalizing vitamin D and/or mineral homeostasis. Thus, hypervitaminosis *D* due to an increased 1α-hydroxylase activity seems to be a cause of the premature aging.

In several studies, we have described that a complete or partial lack of vitamin D action (VDR−/− mice and CYP27B1−/−) show almost similar phenotype as FGF23−/− or Klotho−/− mice. VDR mutant mice have growth retardation, osteoporosis, kyphosis, skin thickening and wrinkling, alopecia, ectopic calcification, progressive loss of hearing and balance as well as short lifespan. CYP27B1−/− mice do not show alopecia nor balance deficit, which might be apoVDR-dependent or calcidiol-dependent. The features are typical to premature aging. The phenotype is resistant to a normalization of the mineral homeostasis by a rescue diet containing high calcium and phosphate. Taken together, aging shows a U-shaped dependency on hormonal forms of vitamin D suggesting that there is an optimal concentration of vitamin D in delaying aging phenomena.

Our recent study shows that calcidiol is an active hormone. Since serum calcidiol but not calcitriol is fluctuating in physiological situations, calcidiol might determine the biological output of vitamin D action. Due to its high serum concentration and better uptake of calcidiol-DBP by the target cells through the cubilin–megalin system, calcidiol seems to be an important circulating hormone. Therefore, serum calcidiol might be associated with an increased risk of aging-related chronic diseases more directly than calcitriol.

Aging and cancer seem to be tightly associated phenomena. Accumulation of damage on DNA and telomeres cause both aging and cancer, moreover the signalling pathways seem to converge on tumour suppressor protein, p53, which seems to be regulated by vitamin D. Also, the insulin-like growth factor signalling pathway (IGF-1, IGFBPs, IGFR) and fibroblast growth factor-23 (FGF-23) regulate growth, aging and cancer. Vitamin D can regulate these signalling pathways, too. Also NF-κB and telomerase reverse transcriptase (TERT) might be molecular mechanisms mediating vitamin D action in aging and cancer.

Calcidiol serum concentrations show a U-shaped risk of prostate cancer suggesting an optimal serum concentration of 40–60 nmol/L for the lowest cancer risk. Therefore, it is necessary to study several common aging-associated diseases such as osteoporosis, hypertension and diabetes known to be vitamin D-dependent before any recommendations of an optimal serum concentration of calcidiol are given.

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1. Introduction

Aging is a complex biological process at molecular, cellular and organismal level. It is generally characterized by the declining ability to respond to stress, increasing homeostatic imbalance and an increased risk of aging-associated diseases. Although the cellular and DNA damages accumulating with time might be the cause of aging and cancer, the weakening cellular repair mechanisms play an important role [1]. On the other hand, hormonal decline has also thought to be important for aging [2–4]. Sex steroids (androgens and estrogens) are known to decrease gradually with aging and might be involved in the aging. Aging of the skin is dependent on the serum level of sex steroids [5]. Hormonal forms of vitamin D also decline with advancing age due to decreased synthesis and increased degradation [6]. Other hormones such as insulin-like growth factor-1 (IGF-1) and fibroblast growth factor-23 (FGF-23) are involved in aging processes, too [1,7]. IGF-1 and serum calcidiol seem to be clinically clearly associated and involved in the development of the metabolic syndrome, which can be regarded

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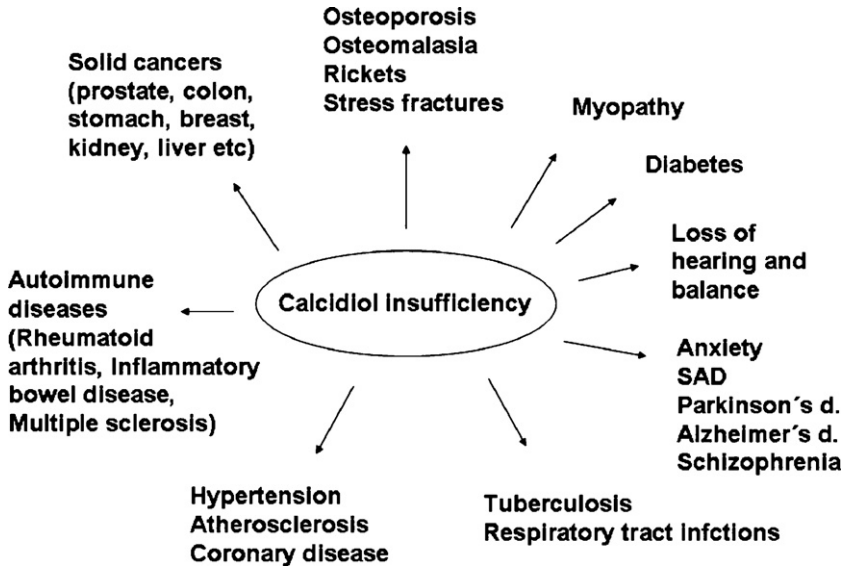

Fig. 1. Vitamin D (calcidiol) insufficiency is associated with an increased risk of several chronic diseases.

as an aging-related disease [8,9]. During the past 10 years, there has been accumulating evidence that a high vitamin D_3 activity is the key mediator of premature aging [6,7,10–15]. It seems that an excess production of calcitriol plays a crucial role in the aging caused by the FGF-23 mutation [14]. All the aging characteristics can be completely reversed by normalizing the serum calcitriol concentration and almost completely by normalizing the mineral homeostasis.

Rickets, osteomalasia, osteoporosis and bone fractures are the well-known outcomes of vitamin D_3 insufficiency or deficiency [16–18]. Furthermore, vitamin D_3/calcidiol insufficiency appears to be associated with several aging-related, chronic diseases [19] (summarized in Fig. 1). This is a review of literature and of our own studies related to high or low vitamin D_3 action and development of premature aging or aging-related diseases.

2. Both calcidiol and calcitriol are active hormones

It seems that calcidiol reflects better the clinical situations than calcitriol, but calcidiol according to present paradigm is an inactive prohormone, whereas calcitriol is an active hormone. The discrepancy was not understandable before our recent study [20] suggesting that both are active hormones and act together. The present paradigm, that circulating calcitriol is the active hormone and 25-hydroxyvitamin D_3 needs to be activated within the cell through the action of 1α-hydroxylase (CYP27B1) [21], could be seriously criticised: (A) Only calcidiol can enter the target cell through megalin-mediated endocytosis of the vitamin D binding protein (DBP) calcidiol complex [22,23], therefore the free circulating calcitriol is hormonally less significant. Furthermore, there is a direct correlation between the megalin-mediated endocytosis and the action of calcidiol [23]. (B) The physiological concentration of calcidiol is ~1000-fold greater than that of calcitriol. The *in vitro* studies usually compare the responses at equal concentrations. (C) The competitive Scatchard VDR binding analysis shows 100–700-fold higher affinity for calcitriol than calcidiol, but Ki as bonded energy suggests significantly smaller difference between calcidiol and calcitriol: 0.07 and 0.03 nmol, respectively [24]. Therefore, the receptor appears to be mainly occupied with calcidiol *in vivo*. If calcidiol would be inactive, it would *in vivo* act as a competitive inhibitor for calcitriol. (D) The intracellular 1α-hydroxylase activity is too slow to explain the relatively rapid biological response. Furthermore, the intracellular calcitriol concentration (<50 pM) [25] is too low to cause any biological response and it is effectively down-regulated by the action of 24-hydroxylase. *In vitro*, toxic concentrations (10–100 nM) of calcitriol are needed for a response in all cell culture experiments. (E) When calcidiol is converted intracellularly to calcitriol, the converted calcitriol is acting as an intracrine regulator and it cannot be called hormone.

Recently, we showed evidence that calcidiol could be an active hormone [20]. It causes a significant growth inhibition of the human prostatic stromal cells at a high physiological concentration (250 nM), whereas pharmacological (toxic) concentrations of calcitriol (10 nM) were needed for the same effect. Vitamin D responsive gene, CYP24 (24-hydroxylase), was clearly induced by calcidiol at 100–250 nM. Since calcitriol has a higher affinity than calcidiol to the enzyme, it is easily hydroxylated and therefore its intracellular and extracellular concentrations stay at a low level (50–150 pM). It seems that calcidiol is mainly controlling the intracellular level of calcitriol through 24-hydroxylase induction. A high expression of CYP24 can lead to a vitamin D resistance, since both metabolites are inactivated. It was proposed that CYP24 were oncogenic, because its overexpression in cancer may result in vitamin D resistance [26]. When using inhibitors of 24-hydroxylase, VID-400, or of 1α-hydroxylase, SDZ88-357, the effect of calcidiol was not inhibited but instead enhanced suggesting an inherent hormonal activity of calcidiol [20]. Since, in physiological situations, serum calcitriol concentration is rather stabile, whereas concentration of calcidiol varies, we conclude that calcidiol might be the key hormone regulating the physiological balance and it might be directly involved in the development and/or progression of aging, chronic diseases and cancers [19]. Calcidiol and calcitriol seem to act within the target cell together, but calcitriol might be more involved in the regulation of intracellular and extracellular calcium balance through parathyroid hormone. We propose that calcidiol is a hormone *de facto*, whereas calcitriol may act both as a hormone and as an intracrine regulator. The difference between the present hypothesis and our new hypothesis is depicted in Fig. 2. An important consequence of the new hypothesis is that it helps to understand the above mentioned discrepancies in vitamin D action as well as it explains, why serum calcidiol more often than calcitriol is associated with chronic diseases and aging as well as with clinical outcome of vitamin D treatment.

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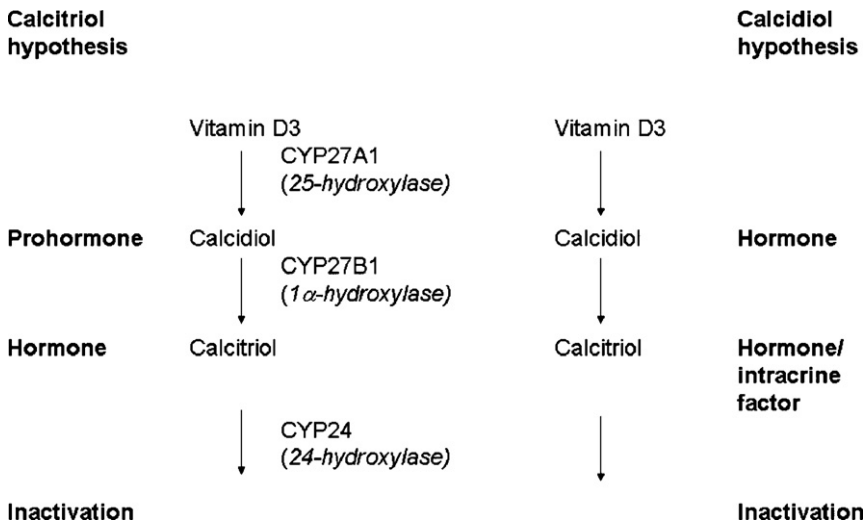

Fig. 2. The prevailing "calcitriol" hypothesis claims that calcidiol is an inactive prohormone, which is activated to the active hormone by CYP27B1 (1α-hydroxylase). Since calcitriol has a 10-fold lower binding affinity to DBP than calcitriol and thus calcitriol is poorly internalized by megalin, therefore calcitriol has to be produced within the target cell meaning that calcitriol is an intracrine factor. Lou et al. [20] have demonstrated an inherent hormonal activity of calcidiol suggesting hormonal "calcidiol" hypothesis.

3. Aging and cancer are closely associated

The aging process is influenced by the environment and by the genetic factors. Peto stated in1985 that there is no such thing as aging, and cancer is not related to it [27]. Recent findings support his view that cancer and aging are closely linked (reviewed by Irminger-Finger [1]). On the cellular level, aging and carcinogenesis is thought to be due to an accumulation of damages especially on DNA. Reactive oxygen species are involved in carcinogenesis, aging and DNA and protein damages [28,29]. Normal VDR activity can protect colonic cells against the oxidative stress [30].

The length of telomeres plays a role in aging and carcinogenesis. Signalling from short telomeres leads to aging [31] and long telomeres can delay aging [32]. The inducible RNA subunit of telomerase is only expressed in stem cells. Cancer cells acquire the capacity of expressing telomerase and, therefore, are immortal [33]. Combined treatment with calcitriol and 9-cis-retinoic acid directly inhibits human telomerase reverse transcriptase (hTERT) [34].

Activation or overexpression of tumour suppressor protein, p53, may lead to cellular aging [35] and its inactivation or low expression to cancer [36]. Calcitriol seems to upregulate p53 expression [37,38]. In agreement, we found a low expression of p53 in absence of vitamin D action (VDR-KO) in aging mice [39]. Since there is an increased risk of several solid cancers, when serum calcidiol is low (see below), it is possible that a low p53 expression might mediate the risk. Interestingly, p53, in turn, seems to regulate VDR expression [40].

An important mechanism of aging and cancer is the growth hormone (GH)/insulin-like growth factor (IGF) signalling system affecting glucose metabolism (reviewed by Irminger-Finger [1]). Primary or secondary IGF-1 deficiency has been implicated in shortening of lifespan [41], however, in man, it can increase the lifespan due to the protection from cancer. Thus, it seems that IGF-1 signalling plays a different role in man and animals as to the aging and carcinogenesis. Vitamin D can regulate expression of the binding protein IGF-BP-3 [42] and thereby IGF-1 activity. In man, there is an inverse association between calcidiol and serum IGF-1 with metabolic syndrome [9]. In VDR-KO mice, we did not find changes in IGF-1 expression, but the expression of IGF-1 receptor was decreased suggesting that vitamin D might regulate IGF-1 signalling system [39]. It has been shown earlier that calcitriol can upregulate IGFR [43].

The transcription factor NF-κB is strongly associated with aging [44] and carcinogenesis [45]. NF-κB controls the expression of many target genes involved in innate and adaptive immunity, inflammation, apoptosis and senescence [46]. The longevity factor, SIRT-1, seem to regulate the efficiency of the NF-κB signalling [47]. We found a decreased expression of NF-κB in VDR-KO mice [39]. In conclusion, the molecular mechanisms mediating aging and carcinogenesis seem to be closely linked and many of them are regulated by hormonal forms of vitamin D_3.

4. Hypervitaminosis D_3 and aging

During the past 10 years, Klotho [10–12] and fibroblast growth factor 23 (FGF-23) [14] have become key mediators of early aging and their effects appear to be mediated by an excess of calcitriol [14,15]. The early aging phenotype includes thin skin, intestinal atrophy, spleen atrophy, muscle atrophy, weight loss, short life span, osteoporosis and ectopic calcification in blood vessels (atherosclerosis). Because of the tight control of hormonal forms of vitamin D_3 by 24-hydroxylase, which is induced by high physiological concentrations of calcidiol [20], hypervitaminosis D_3 is rare in humans. Therefore, its influence on aging has not been extensively studied. Sarcoidosis is a rare disease affecting many organs especially lungs, skin, eyes and immune system [48]. In some sarcoidosis patients, lung macrophages overproduce calcitriol, which may cause a severe hypercalcemia and a panhypopituitarism with unaffected prolactin secretion [49]. The disease is, however, a periodic and a time-limited disease, therefore premature aging phenotype has not been found. In Crohn's disease, hypercalcemia due to excess of calcitriol has also been found, but premature aging has not been described [50]. During the early period of vitamin D substitution some intoxications occurred; after the Second World War in Europe especially in Germany and DDR, children received extremely high oral doses of vitamin D and suffered hypercalcemia, early aging, cardiovascular complications and early death suggesting that hypervitaminosis D can accelerate aging.

5. Hypovitaminosis D and aging

It has been demonstrated that vitamin D_3 insufficiency can increase the risk of such aging-related diseases as osteoporosis [16–18], cancers [51], muscle weakness [52,53], respiratory infections [54], autoimmune diseases [55], diabetes [56], hypertension

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Table 1
Aging features associated with hyper- and hypovitaminosis D (Tuohimaa [19], Kuro-o et al. [10], Dardenne et al. [89], Razzaque et al. [14] and Keisala et al. [39]).

Aging feature	Hypervitaminosis		Normovitaminosis	Hypovitaminosis	
	FGF-23−/−	Klotho−/−	WT	VDR−/−	CYP27B1−/−
Short lifespan	+	+	−	+	+
Small body weight	+	+	−	+	+
Kyphosis	+	+	−	+	−
Osteoporosis	+	+	−	+	+
Loss of hair	+	+	−	+	−
Skin atrophy	+	+	−	−	−
Skin wrinkles	−	−	−	+	−
Muscle atrophy	+	+	−	+	?
Intestine atrophy	+	+	−	?	?
Immunodeficiency	+	+	−	+	+
Hypogonadism	+	+	−	+	?
Infertility	+	+	−	+ (female)	?
Atherosclerosis	+	+	−	−	?
Ectopic calcification	+	+	−	+	+
Loss of hearing	?	?	−	+	?
Loss of balance	?	?	−	+	−

+ = feature present, − = feature not present, ? = not known, not studied.

[57–59], cardiovascular diseases, [60,61] and congestive hearth failure [62] (Fig. 1). Hypovitaminosis D_3 is independently associated with all-cause mortality [63]. Metabolites of vitamin D_3 are also known as neurosteroids regulating e.g. behavioural functions such as anxiety [64], hypovitaminosis is associated with an increased risk of multiple sclerosis [65], seasonal affective disorder (SAD) [66], schizophrenia [67,68], Parkinson's disease and Alzheimer's disease [69]. Chronic calcitriol treatment is able to reduce Ca^{++}-mediated hippocampal biomarkers of aging [70]. Also some double-blind placebo-controlled prevention trials support the hypothesis that vitamin D_3 is significantly involved in several chronic diseases and it could be effectively used in preventive medicine [71].

We have found a premature aging phenotype in mice with mutated vitamin D receptor (VDR-KO) [39,72,73]. These mice survive only when they are fed with special calcium-rich diet. After 6 months of age, they show symptoms of premature aging such as wrinkling of the skin, hair and weight loss, muscle atrophy, immunological deficiency [74] osteoporosis and ectopic calcification in the thalamic area of the brain [73]. Furthermore, the VDR-KO mice developed hearing and balance defect earlier than the wild-type littermates [75,76]. These results suggest that mice with vitamin D imbalance show symptoms of early aging. The early aging appears with low and high activity of D hormones being, thus, U-shaped risk in relation to hormonal activity of vitamin D metabolites (Table 1).

6. Vitamin D and cancer

Numerous *in vitro* and *in vivo* studies have shown that vitamin D potently inhibits cell proliferation in a wide range of normal cell types and carcinomas such as cancer of the mammary gland, prostate, colon, skin and brain, myeloid leukaemia cells and many others [77]. Epidemiological studies suggest that nearly 20 types of cancer are inversely correlated with solar ultraviolet-B levels or with the availability of vitamin D [78]. Several studies *in vitro* suggest that hormonal forms of vitamin D_3 can regulate their mitotic activity and differentiation of cancer cells (for a review see [79]). Mechanisms include regulation of the immune responses, expression of growth inhibitory factors, a direct regulation of cell cycle as well as the invasion of cancer cells [80]. They are most likely mediated by the nuclear vitamin D receptor, but the effect of other steroid receptors such as glucocorticoid and thyroid receptors cannot be excluded, because calcidiol and calcitriol can bind firmly to them [24].

Exposure to sun light, serum concentrations of calcitriol and calcidiol seem to be inversely associated with an increased cancer risk, although the results are not consistent (for review see Tuohimaa [19]. The reason for the discrepancies is not known, but it might be due to different geographic location, assay methods, age distribution and small sample sizes. We made a case-control study of 19,000 Finnish men [81]. Prostate cancer risk was inversely related to calcidiol. Men with calcidiol concentration below 40 nmol/L had an adjusted relative risk of 1.7 compared with men with calcidiol above 40 nmol/L. Prostate cancer risk was highest (3.5) among younger men with low calcidiol. The mean age at the diagnosis was 1.8 years lower in men with low calcidiol and the cancer was more aggressive. The risk of prostate cancer increased up to eightfold, when three factors of metabolic syndrome were combined with the low calcidiol serum concentration [82]. Since the material in the previous studies did not allow a detailed analysis, we conducted a larger scale longitudinal nested case-control study on a Nordic serum bank of 200,000 samples [83]. It included 622 prostate cancer cases and 1451 matched controls. It was found that both low (<19 nmol/L) and high (>80 nmol/L) levels of calcidiol serum concentrations were associated with higher risk of prostate cancer. The normal average serum concentration of calcidiol (40–60 nmol/L) comprises the lowest risk. Thus, the risk of prostate cancer associated with serum calcidiol is U-shaped as the aging phenotype above. Therefore, the proposals for recommendations of vitamin D intake [84,85] should be re-evaluated and based on several diseases, not only osteoporosis.

If the hypothesis on the role of calcidiol in cancer were valid, it could be expected, that the risk of some cancers would be reduced after skin cancers, since skin cancers possibly could be used a marker of a high sun exposure. The high sun exposure would produce more vitamin D, which would protect against some solid cancers. This effect should be stronger in countries with high solar exposure throughout the year. To elucidate this hypothesis, we studied the joined occurrence of skin cancers and other primary cancers from 13 cancer registries [86]. The material consisted of 416,134 cases of skin cancer and 3,776,501 cases of non-skin cancer as a first cancer. After the primary skin cancer including melanoma, basal and squamous cell carcinoma there was a reduced risk of all solid cancers, but only the sunny countries (Spain, Singapore and Australia), but not in the Nordic countries. A clear protective effect of sun exposure was found for 9 cancers (stomach, colorectum, liver and gallbladder, pancreas, lung, mammary gland, prostate, bladder and kidney). Similar results have been recently obtained

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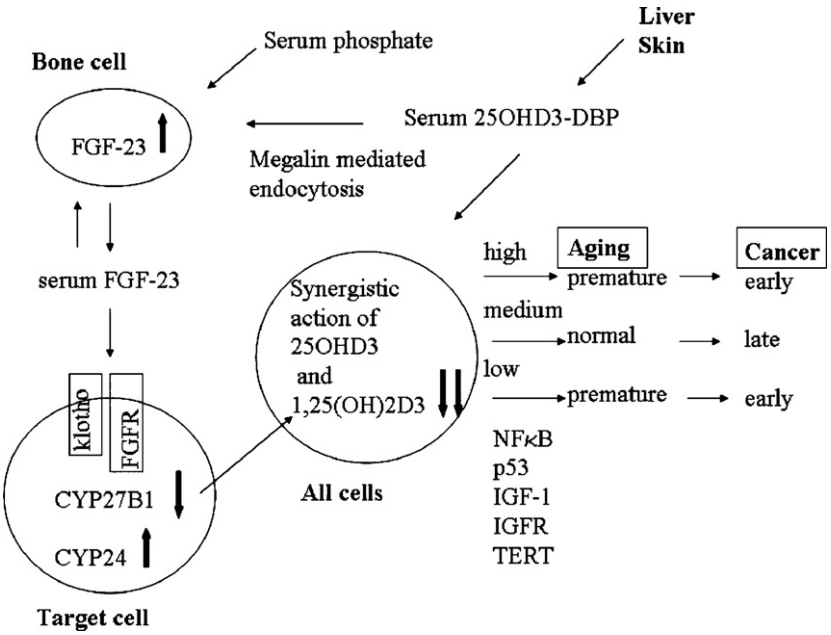

Fig. 3. Hormonal forms of vitamin D_3 and premature aging. Serum calcidiol (25OHD3) bound to vitamin D binding protein (DBP) enters the cell through megalin-mediated endocytosis and can be converted to calcitriol (1,25(OH)2D3) by 1α-hydroxylase (CYP27B1). This leads to an increased expression of FGF-23, which in turn suppresses the intracellular concentration of calcitriol by a decreased expression of 1α-hydroxylase and by an increased degradation via 24-hydroxylase. Intracellular concentration of calcidiol is dependent on its serum concentration, therefore it remains unaffected. The action of calcitriol and calcidiol consist of autocrine and endocrine systems. The total synergistic activity of calcidiol and calcitriol within the cell is, therefore, regulated by the intracellular concentration of calcitriol and extra-/intracellular concentration of calcidiol. Both a high and low action of calcidiol and calcitriol lead to a premature aging with early development of aging associated diseases (e.g. cancer). Several aging-related genes (NFκB, p53, Growth hormone/IGF-1 signalling and TERT) appear to be vitamin D-regulated (for the details see text). Modified from Kuro-o [7] and Tuohimaa [19].

for prostate cancer [87] and for several cancers in a meta-analysis of second cancers after a diagnosis of non-melanoma skin cancer [78]. Childhood sunburns are a risk for melanoma, but they seem to protect against prostate cancer in adulthood [88].

It can be concluded that a low serum concentration of calcidiol seems to be a risk factor for many solid cancers. Whether also a high serum concentration of calcidiol is a similar risk factor needs to be studied further for other cancers than prostate especially because an excess of hormonal forms of vitamin D seems to accelerate premature aging, which, in turn, is tightly associated with carcinogenesis as described above.

7. Conclusions

In conclusion, an aging hypothesis based on hypo- or hypervitaminosis D is proposed (Fig. 3). The risk of aging related diseases, especially that of cancer is dependent on general aging processes and therefore they appear earlier during a vitamin D imbalance. Because of the high serum concentration, calcidiol instead of calcitriol appears to be the main circulating hormone, which only can enter the target cells through megalin–cubilin system and which can be converted in all cells to calcitriol. Intracellular calcitriol as an intracrine regulator may act together with calcidiol regulating aging-related genes (FGF-23, p53, NF-κB, IGFBPs, IGFR and TERT). Because the serum concentration of calcidiol shows a U-shaped association with risk of (prostate) cancer and aging, it can be assumed that there is an optimal serum concentration for general health. Therefore bone health cannot be the only criterion when it is determined. An important task for the future studies is to find the optimal serum calcidiol concentration in different chronic diseases.

Acknowledgements

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